CASE 4-30811A/C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



IN RE APPLICATION OF

MATTHEWS ET AL.

APPLICATION NO: N/A

FILED: Herewith

FOR: SPONTANEOUSLY DISPERSIBLE N-BENZOYL STAUROSPORINE COMPOSITIONS

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of British Application No. 9903547.9, filed on February 16, 1999. This application is acknowledged in the Declaration of the instant case.

The certified copy of said British application is submitted herewith.

Respectfully submitted,

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Date: August 14, 2001

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4-30811 P1 (2)

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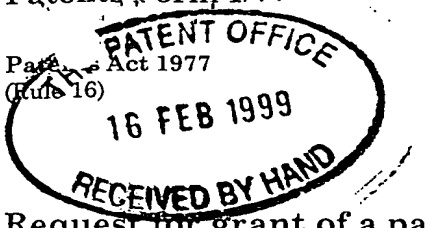


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| | **9903547.9** *(rt)* | 16 FEB 1999 17FEB99 E425996-4 D00524 P01/7700 0.00 - 9903547.9 |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | NOVARTIS AG<br>SCHWARZWALDALLEE 215<br>4058 BASEL<br>SWITZERLAND |
| | Patent ADP number *(if you know it)* | 7125487002 |
| | If the applicant is a corporate body, give the country/state of its incorporation | SWITZERLAND |
| 4. | Title of invention | Organic compounds |
| 5. | Name of your agent *(If you have one)* | |
| | "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | B.A. YORKE & CO.<br>CHARTERED PATENT AGENTS<br>COOMB HOUSE, 7 ST. JOHN'S ROAD<br>ISLEWORTH<br>MIDDLESEX TW7 6NH |
| | Patents ADP number *(if you know it)* | 1800001 |

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Organic Compounds

The present invention relates to novel pharmaceutical compositions in which an active agent is N-benzoyl-staurosporine as disclosed e.g. in US 5,093,330 and equivalents thereof.

N-benzoyl-staurosporine presents highly specific difficulties in relation to administration generally and pharmaceutical compositions in particular, including problems with drug bioavailability and variability in inter- and intra-patient dose response. We have found it to be very lipophilic and practically insoluble in water, in simulated gastric and in intestinal fluids (solubility <0.1 mg/L). In particular this exceptional low solubility of the active substance necessitated development of a non-conventional dosage form.

In accordance with the present invention it has now surprisingly been found that stable pharmaceutical compositions with N-benzoyl-staurosporine having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters are obtainable. These novel N-benzoyl-staurosporine compositions have been found to meet or substantially reduce the difficulties encountered previously. It has been shown that the compositions in accordance with the present invention may enable effective N-benzoyl-staurosporine dosaging with concomitant enhancement as well as reduced variability of resorption/bioavailability levels for and between individual patients. More particularly, it has been found that these compositions may contain solubilized N-benzoyl-staurosporine in sufficiently high concentration to permit convenient oral administration without exhibiting precipitation of the active agent. Thus, the invention may achieve effective therapy with lower N-benzoyl-staurosporine dosage levels and may permit closer standardization and optimization of daily dosage requirements for each individual. Consequently, occurrence of undesirable side-effects is diminished and overall cost of therapy may be reduced.

In one aspect the present invention provides a spontaneously dispersible pharmaceutical

composition for enteral, e.g. oral, administration comprising N-benzoyl-staurosporine, for example in the form of a micellar precursor.

The term spontaneously dispersible pharmaceutical composition as used herein is defined as a system that is capable of producing colloidal structures, e.g. droplets, particles and/or micelles, of up to 1000 nm, when diluted with an aqueous medium. The aqueous medium may be for example water, for example on dilution of e.g. 1:10, or gastric juices, e.g. simulated conditions after oral application. The colloidal structures, e.g. droplets, particles and/or micelles, are formed spontaneously or substantially spontaneously when the components of the dispersible pharmaceutical composition are brought into contact with an aqueous medium, e.g. by simple shaking by hand for a short period of time, for example for 10 seconds. Such spontaneously dispersible pharmaceutical compositions are thermodynamically stable, e.g. from at least 15 minutes or 4 hours to 24 hours. Typically, they contain dispersed, e.g. colloidal structures of a size less than about 200 nm as measured by standard light scattering techniques, e.g. using a Malvern Zetasizer 3000, preferably they comprise droplets or particles having a mean diameter of less than about 150 nm, typically less than 100 nm, generally greater than 5 nm. The micellar compositions or the micellar part of such spontaneously dispersible compositions may be monophasic and substantially non-opaque, i.e. transparent or opalescent when viewed by optical microscopic means.

Alternatively, the spontaneously dispersible pharmaceutical composition may form simultaneously a mixture comprising aqueous micelles and nanoparticles. Such nanoparticles may have a particle size of from 150 nm to about 1000 nm, generally in the range of 200 to 800 nm. It was found that the amount of nanoparticles produced may be temperature dependent but still adequate bioavailability characteristics may be obtained.

In another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising

1) N-benzoyl-staurosporine,

2) a hydrophilic component, and

3) a surfactant.

The spontaneously dispersible pharmaceutical composition (hereinafter embraced by the term pharmaceutical composition of the present invention) is preferably in the form of a colloidal structure, e.g. a micellar precursor. N-benzoyl-staurosporine is hereinafter also referred to as the active agent and all other components of the spontaneously dispersible pharmaceutical composition may be hereinafter referred to as the carrier medium of the spontaneously dispersible pharmaceutical composition. The components of the spontaneously dispersible pharmaceutical compositions may be described in Fiedler, H. P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor, D-7960 Aulendorf, 4th revised and expanded edition (1996), the contents of which are hereby incorporated by reference.

In accordance with the present invention N-benzoyl-staurosporine may be present in an amount by weight of up to about 20% by weight of the composition. Preferably the active agent is present in an amount of 1 to 15% by weight of the composition, for example about 5 to 10%, and more preferred 5%.

The hydrophilic component preferably provides for fast mixing of the active agent with water on admixture with water and may be determined by routine experimentation, for example by various chromatography methods, e.g. Gas Chromatography (GC). The hydrophilic component may comprise a main or sole component, e.g. an alcohol, e.g. ethanol, or alternatively may comprise a co-component which may be selected from partial ethers or lower alkanols. Preferred lower alkanol components include ethanol, 1,2-propylene glycol or a polyethylene glycol, e.g. of a molecular weight of 100 to 600 daltons, e.g. polyethylene glycol 400. When present in the invention ethanol may comprise up to 60 % by weight of the hydrophilic component; preferably 20 to about 55% by weight, more preferably about 25 to about 40 % by weight. Especially preferred partial ethers are those known and commercially available as for example glycofurol (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether). These co-components when present

are e.g. a partial replacement of other components of the hydrophilic component such that the efficacy of the hydrophilic component as part of the N-benzoyl-staurosporine carrier medium is not materially impaired. The hydrophilic component may further comprise triethylcitrate, Transcutol, N-methylpyrrolidone, dimethylisosorbide, or propylene carbonate.

The total amount of the hydrophilic component present in the spontaneously dispersible pharmaceutical compositions of the present invention may comprise 5 to 50% by weight of the carrier medium, e.g. 10 to 50%; preferably 10 to 40% by weight, more preferably about 15 to 35 % by weight.

Pharmaceutical compositions of the present invention further comprise at least one pharmaceutically acceptable surfactant. Surfactants useful for the present invention may be of the anionic, cationic, amphoteric or non-ionic type or mixtures thereof and have generally a hydrophilic-lipophilic balance (HLB) value of from about 3 to 20. Usually nonionic surfactants are preferred, particularly those non-ionic surfactants that have an HLB value of greater than 10, e.g. 14 to 20. Alternatively, the pharmaceutical compositions of the present invention may embrace systems comprising a mixture of surfactants, e.g. a mixture of a first surfactant and one or more co-surfactants selected from any of the surfactant types listed below. Especially preferred are specific combinations of a surfactant having a high HLB value with a co-surfactant having a low HLB value, for example a combination of a polyoxyethylene castor oil derivative, e.g. Cremophor RH 40 (HLB 14-16) and a transesterified ethoxylated vegetable oil, e.g. Labrafil M2125 CS (HLB 3-4).

Particularly preferred surfactants of high HLB value, e.g. HLB > 10, are the following:

(i) Reaction products of a natural or hydrogenated vegetable oil and ethylene oxide, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. The natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from

about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various of such surfactants are commercially available. The polyethyleneglycol hydrogenated castor oils available under the trade name CREMOPHOR are especially suitable (Fiedler, loc. cit., 1, p. 392-395). Particularly suitable are CREMOPHOR RH 40, which has a saponification number of about 50 to 60, an acid number less than about 1, a water content (Fischer) less than about 2%, an $n_D^{60}$ of about 1.453 to 1.457 and an HLB of about 14 to 16; and CREMOPHOR RH 60, which has a saponification number of about 40 to 50, an acid number less than about 1, an iodine number of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an $n_D^{25}$ of about 1.453 to 1.457 and an HLB of about 15 to 17. An especially preferred product of this class is CREMOPHOR RH40. Also suitable are polyethyleneglycol castor oils such as that available under the trade name CREMOPHOR EL, which has a molecular weight (by steam osmometry) of about 1630, a saponification number of about 65 to 70, an acid number of about 2, an iodine number of about 28 to 32 and an $n_D^{25}$ of about 1.471 and an HLB value of about 12 to 14. Also suitable are the various tensides available under the trade names NIKKOL (e.g. NIKKOL HCO-40 and HCO-60), MAPEG (e.g. MAPEG CO-40h), INCROCAS (e.g. INCROCAS 40), and TAGAT, for example polyoxyethylene-glycerol-fatty acid esters, e.g. TAGAT RH 40, and polyoxyethylene-glycerol-trioleates, e.g. TAGAT TO having a HLB value of 11.3. These surfactants are further described in Fiedler loc. cit..

(ii) Related products that belong to the class of polyoxyethylene alkyl ethers are available under the tradename BRIJ, e.g. Brij 35 which has an HLB value of about 16.9.

(iii) Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name MYRJ (Fiedler, loc. cit., 2, p.1042-1043). An especially preferred product of this class is MYRJ 52 having a $n_D^{25}$ of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9, an acid value of about 0 to 1 and a saponification no. of about 25 to 35. Other related products include polyethoxylated saturated hydroxy fatty acids which may be

produced by reacting a saturated hydroxy fatty acid, e.g. $C_{18}$ to $C_{20}$ with e.g. ethylene oxide or polyethylene glycol. Suitable examples for the present invention include are known and commercially available, e.g. from the BASF company under the trade mark Solutol. Especially preferred is Solutol HS15 which is known, e.g. from the BASF technical leaflet MEF 151E (1986), to comprise of about 70% polyethoxylated 12-hydroxystearate by weight and about 30% by weight unesterified polyethylene glycol component. Solutol HS 15 has a hydrogenation value of 90 to 110, a saponification value of 53 to 63, an acid number of maximum 1, and a maximum water content of 0.5% by weight.

(iv) Polyoxyethylene-sorbitan-fatty acid esters (also called polysorbates), for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type known and commercially available under the trade name TWEEN (Fiedler, loc. cit., 2, p.1615-1619) including the products TWEEN

20 [polyoxyethylene(20)sorbitanmonolaurate] with an HLB of about 16.7,
21 [polyoxyethylene(4)sorbitanmonolaurate] with an HLB of about 13.3,
40 [polyoxyethylene(20)sorbitanmonopalmitate] with an HLB of about 15.6,
60 [polyoxyethylene(20)sorbitanmonostearate] with an HLB of about 14.9,
65 [polyoxyethylene(20)sorbitantristearate] with an HLB of about 10.5,
80 [polyoxyethylene(20)sorbitanmonooleate] with an HLB of about 15.0,
81 [polyoxyethylene(5)sorbitanmonooleate] with an HLB of about 10.0,
85 [polyoxyethylene(20)sorbitantrioleate] with an HLB of about 11.0.

Especially preferred products of this class are TWEEN 40 and TWEEN 80.

(v) Tocopherol esters, e.g. tocopheryl acetate and tocopheryl acid succinate (HLB of about 16).

(vi) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, for example of the type known and commercially available under the trade names PLURONIC, EMKALYX and POLOXAMER (Fiedler, loc. cit., 2, p. 1198-1204). An especially preferred product of this class is PLURONIC F68, having a melting point of about

52°C and a molecular weight of about 6800 to 8975. A further preferred product of this class is POLOXAMER 188, which has an HLB value of about 29.

Particularly preferred co-surfactants having a low HLB value, e.g. HLB < 10, are the following:

(i) Sorbitan fatty acid esters, e.g. of the type known and commercially available under the trade name Span, for example including sorbitan-monolaureyl ester (HLB 8.6), -monopalmityl ester (HLB 6.7), -monostearyl ester (HLB 4.7), -tristearyl ester (HLB 2.1), -monooleyl ester (HLB 4.3), and -trioleyl esters (HLB 1.8) (Fiedler, loc. cit., 2, p. 1430).

(ii) Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (also known and commercially available under the trade name MIGLYOL 840), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (Fiedler, loc. cit., 2, p. 1008-1010). Propylene glycol mono $C_8$ esters include Sefsol 218 (Nikko Chemicals) and Capryol 90 (Gattefossè).

(iii) Transesterified ethoxylated vegetable oils such as those obtained by reacting various natural vegetable oils (for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil, or mixtures thereof) with polyethylene glycols that have an average molecular weight of from 200 to 800, in the presence of an appropriate catalyst (according to known procedures described in the literature, e.g. US Patent 3 288 824). Transesterified ethoxylated corn oil is particularly preferred. Various forms of transesterified ethoxylated vegetable oils are known and commercially available under the trade name LABRAFIL (Fiedler, loc cit, 2, p. 880). Especially suitable examples are LABRAFIL M 2125 CS (obtained from corn oil and having an acid number of less than about 2, a saponification number of 155 to 175, an HLB value of 3 to 4, and an iodine number of 90 to 110), and LABRAFIL M 1944 CS (obtained from kernel oil and having an acid number of about

2, a saponification number of 145 to 175 and an iodine number of 60 to 90). LABRAFIL M 2130 CS (which is a transesterification product of a $C_{12-18}$ glyceride and polyethylene glycol and which has a melting point of about 35 to 40°C, an acid number of less than about 2, a saponification number of 185 to 200 and an iodine number of less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is LABRAFIL M 2125 CS which can be obtained, for example, from Gattefossè, Saint-Priest Cedex, France.

(iv) Mono-, di-and mono/diglycerides, e.g. $C_8$ to $C_{10}$ fatty acid mono- and di-glycerides include Capmul MCM, Akoline MCM (from the Karlshamns company), Imwitor 308 and Imwitor 988, which have an HLB value of about 3.8 (from the Contensio company), and especially esterification products of caprylic or capric acid with glycerol. Preferred products are of this class are e.g. those comprising or essentially consisting of caprylic/capric acid mono- and di-glycerides. $C_8$ to $C_{10}$ mono-, di-glycerides having 6 to 10 mol-% polyoxyethylene groups, e.g. Softigen 767 (available from Contensio Chemicals). Monoglycerides, e.g. monooleate, glycerol monopalmitate and glycerol monostearate, for example as known and commercially available under the trade names Myvatex, Myvaplex, and Myverol (Fiedler, loc. cit., 2, p. 1044) and acetylated, e.g. mono- and di-acetylated monoglycerides, for example as known under the trade name Myvacet (Fiedler, loc. cit., 2, p. 1043).

(v) Pentaerythriol fatty acid esters and polyalkylene glycol ethers and polyalkylene glycol ethers, for example pentaerythrite-dioleate, -distearate, -monolaurate, -polyglycol ether, and -monostearate as well as pentaerythrite-fatty acid esters (Fiedler, loc. cit., 2, p. 1158-1160)

(vi) Other suitable surfactants include glycerol triacetate or (1,2,3)-triacetin (Fiedler, loc. cit., 2, p. 1580); and sterols and derivatives thereof.

Further ionic surfactant classes not represented by the categories described above include

(i) Docusate salts, for example dioctylsulfosuccinate or related compounds, for example di-[2-ethylhexyl]-succinate (Fiedler, loc. cit., 1, p. 500).

(ii) Phospholipids, in particular lecithins (Fiedler, loc. cit., 2, p. 910-912). Lecithins suitable for use in the compositions of the invention include, in particular, soya bean lecithins.

Thus, in another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant selected from the group consisting of polyoxyethylenes, for example a polyoxyethylene castor oil, e.g. Cremophor RH40, a polyoxyethylene alkyl ether, e.g. Brij 35, polyglycerols and related polyols, for example a polysorbate, e.g. Tween 20, and polyalkylene oxide copolymers, e.g. Pluronic.

Furthermore, in yet another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant having a high HLB value of greater than 10, for example selected form the group consisting of a polyoxyethylene castor oil, e.g. Cremophor RH 40, a polyoxyethylene alkyl ether, e.g. Brij 35, and a polysorbate, e.g. Tween 20, and co-surfactant having a low HLB value of less than 10, for example a transesterified ethoxylated vegetable oil, e.g. Labrafil M2125 CS.

Such spontaneously dispersible pharmaceutical composition may be formulated in a conventional manner and may preferably be in a form of a micellar precursor as described above.

The total amount of surfactant and co-surfactant present in the pharmaceutical composition of the present invention may comprise 5 to 80 % by weight of the carrier medium; preferably 10 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably between about 30 % and 55% by weight.

The pharmaceutical compositions of the present invention may further comprise a lipophilic component. These compositions may be capable of producing emulsions, preferably an aqueous microemulsion, upon mixing with an aqueous medium. Preferably the lipophilic component may be characterized by a low HLB value of less than 10, e.g. up to 8. The lipophilic component may comprise fatty acid triglycerides, preferably medium chain fatty acid triglycerides. Especially suitable medium chain fatty acid triglycerides are neutral oils, e.g. neutral plant oils, in particular fractionated coconut oils, for example those known and commercially available under the trade names Captex, Myritol, Capmul, Neobee and Mazol; Miglyol 812 being the most preferred. Miglyol 812 is a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight = about 520 daltons. Fatty acid composition = $C_6$ max. about 3%, $C_8$ about 50 to 65%, $C_{10}$ about 30 to 45%, $C_{12}$ max 5%; acid no. = about 0.1; saponification no. about 330 to 345; iodine no. = max 1. Miglyol 812 is available from the Hüls company. Other suitable triglycerides preferably comprise mixtures of $C_{8-10}$ or $C_{12-20}$ fatty acid triglycerides, especially $C_{16-18}$ fatty acid triglycerides. The fatty acid component of the triglycerides may comprise both saturated and unsaturated fatty acid residues. Preferably however they are predominantly comprised of unsaturated fatty acid residues; in particular $C_{18}$ unsaturated fatty acid residues. Suitably the triglycerides comprise at least 60%, preferably at least 75%, more preferably at least 85% by weight of a $C_{18}$ unsaturated fatty acid (for example linolenic, linoleic and oleic acid) triglycerides. Suitably the triglycerides comprise less than 20%, for example about 15% or 10% by weight or less, saturated fatty acid (for example palmitic and stearic acid) triglycerides.

The lipophilic comoponent may also comprise a transesterification product, generally obtained as described in GB 2 257 359 or WO 94/09211, the contents of which are incorporated herein by reference. Other particularly suitable triglycerides are the purified transesterification products of corn oil and glycerol, hereinafter referred to as corn oil glycerides and produced according to the description of GB 2 257 359 or WO 94/09211.

Thus, in another aspect, the invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant

having a HLB value of greater than 10 and a fatty acid glyceride as a lipophilic component.

The total amount of lipophilic component when present in the spontaneously dispersible pharmaceutical compositions may comprise 5 to 85 % by weight of the carrier medium, e.g. 10 to 85%; preferably 15 to 70 % by weight, more preferably about 20 to about 50 % by weight.

Accordingly, in yet another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, a surfactant selected from the group consisting of a polyoxyethylene castor oil, e.g. Cremophor RH 40, a polyoxyethylene alkyl ether, e.g. Brij 35, and a polysorbate, e.g. Tween 20, and a lipophilic component selected from the group consisting of a fatty acid glycerides, for example a fractionated coconut oil, e.g. Miglyol 810 and 812, a corn oil glyceride, and a acetylated mono- or diglyceride, respectively.

Such spontaneously dispersible pharmaceutical composition may be formulated in a conventional manner and may preferably be in a form of a micellar precursor as described above.

Where desired, the pharmaceutical compositions of the present invention may comprise further additives or ingredients, for example thickening agents, suspending agents, solidifying agents, as well as antioxidants, e.g. tocopherols, ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), antimicrobial agents, enzyme inhibitors, stabilizers, preserving agents, and the like. The total amount of these additives or ingredients when present in the invention may comprise about 0.05 to 5 %, preferably 0.1 to 1%, by weight of the total weight of the spontaneously dispersible pharmaceutical composition. The spontaneously dispersible pharmaceutical composition may also include sweetening or flavoring agents in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition.

Thus in yet another aspect, the present invention provides a spontaneously dispersible

pharmaceutical composition for oral administration comprising

(a) up to 20% by weight of N-benzoyl-staurosporine,

(b) 5 to 50% by weight of a hydrophilic component,

(c) 5 to 80% by weight of a surfactant or surfactant mixture,

(d) 5 to 85% by weight of a lipophilic component, and

(e) 0.05 to 5 % by weight of an additive.

Naturally, any pharmaceutical composition of the present invention as described above in form of a micellar precursor can itself, i.e. before dilution with an aqueous medium, or after dilution with an aqueous medium, be present in the form of a an aqueous micellar solution (possibly comprising nanoparticles), an oily or aqueous emulsion, preferably a microemulsion, and accordingly exhibit the structural features characteristic of such systems.

The pharmaceutical formulations, e.g. those in the examples hereinafter, may show good stability characteristics as indicated by standard stability trials, for example having a shelf life stability of up to one, two or three years, and even longer. The pharmaceutical formulations of this invention produce aqueous microemulsions or aqueous micelles which are stable for up to one day or longer.

The pharmaceutical compositions of the invention exhibit especially advantageous properties when administered orally. For example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials. These trials are performed in animals e.g. rats or dogs or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the drug substance in the blood. For example, the composition of Example 1 administered p.o. to dogs gives surprisingly high $C_{max}$ average values as detected by ELISA using a specific monoclonal antibody.

Pharmacokinetic parameters, for example absorption and blood levels, also become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. It has been found that the compositions of this invention reduce

variability in inter- and intra-patient dose response. Additionally the pharmaceutical compositions of the present invention are effective with tenside materials, for example bile salts, being present in the gastro-intestinal tract. That is, the pharmaceutical compositions of the present invention are spontaneously dispersible in aqueous systems comprising such natural tensides and thus capable of providing aqueous microemulsion or aqueous micellar systems in situ which are stable. The function of the pharmaceutical compositions in the present invention upon oral administration remain substantially independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual.

In another aspect, the invention provides a process for the production of a spontaneously dispersible pharmaceutical composition as defined above, which process comprises bringing the hydrophilic component and the surfactant (and additional components if required) into intimate admixture, and adding the active agent, i.e. N-benzoyl-staurosporine. When required, the composition may be compounded into unit dosage form, for example by encapsulation into soft or hard gelatine capsules. Optionally further components or additives, in particular a hydrophilic co-component, for example ethanol, may be mixed with the two components or with or after addition of the active agent. For example, while the use of ethanol in the compositions is not essential, ethanol may provide additional benefits, for example it has been found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are improved, in particular the risk of active agent precipitation following encapsulation procedures is reduced. Thus the shelf life stability may be extended by employing ethanol or some other such co-component as an additional ingredient of the hydrophilic component.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of active agent dosages giving equivalent blood levels of active agent; for example using dosages in the range from 25 mg to 300 mg, preferably from 100 to 225 mg, e.g. 150 mg of active agent per day for a 75 kilogram mammal, e.g. an adult human, and in standard animal models.

The increased bioavailability of the active agent provided by the compositions may be observed in standard animal tests and in clinical trials, e.g. as described above.

The pharmaceutical compositions of the present invention are preferably compounded in unit dosage form, for example by filling them into orally administrable capsule shells. The capsule shells may be soft or hard gelatine capsule shells. Where the pharmaceutical composition of the present invention is in unit dosage form, each unit dosage will suitably contain from 25 to 100 mg active agent, preferably between 25 and 75 mg of the active agent, for example 25 or 50 mg. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the component of therapy and the like. However, if desired, the pharmaceutical compositions of the present invention may be in drink solution form and may include water or any other aqueous system, to provide formulations suitable for drinking.

The pharmaceutical compositions of the present invention are particularly useful for treatment and prevention of the conditions disclosed in US 5,093,330, the contents of which are incorporated herein by reference. Most notably, these compositions show high anti-proliferative and anti-tumor activity, as a result of Protein Kinase C (PKC) inhibition, which may be extremely useful for cancer treatment. Moreover, their highly selective and potent inhibition of PKC may lead to superior clinical outcomes for the patient (i.e. delay or suppress disease progression) with equally tolerable regimens. Potential applications include a variety of solid tumors and more specifically for example breast cancer, colon cancer, ovarian cancer and leukemia. In addition, various other indications that may be affected by PKC activity may be effectively treated by these compositions, including Multidrug Resistance (MDR), one of the major problems in currently employed cancer chemotherapy, and inflammatory diseases in general. Thus, in another aspect the present invention provides a method of treatment comprising administering a dispersible pharmaceutical composition according to the present invention to a subject in need of such treatment.

Examples

Following is a description by way of example only of compositions of this invention and are

not intended to limit the scope of the present invention. Particulate measurements, including mean size measurement of dispersed particles (diameter), measured at a 90° scattering angle and a temperature 20°C, were performed using a Malvern Zetasizer 3000. The carrier medium was prepared by mixing the components one with another. The active agent N-benzoyl-staurosporine is then dissolved in the carrier medium by stirring. No phase separation or precipitation is observed for any of the described compositions 1 to 4 which are and remain clear.

| | | *I* | *II* | *III* | *IV* |
|---|---|---|---|---|---|
| ***Co-/Surfactants %(g/g)*** | Cremophor RH 40 | 42.750 | 66.500 | 57.000 | |
| | Solutol HS 15 | | | | 75.905 |
| | Labrafil M2125 CS | | 18.905 | | |
| ***Hydrophilic Component %(g/g)*** | PEG 400 | 25.65 | | | |
| | Propylene Glycol | | 9.500 | 4.750 | 9.500 |
| | Ethanol abs. | 9.500 | | | 9.500 |
| | Triethylcitrate | | | 4.750 | |
| ***Lypophilic Component %(g/g)*** | Corn Oil Glycerides | 17.005 | | 28.405 | |
| ***Other Additives %(g/g)*** | Tocopherol | 0.095 | 0.095 | 0.095 | 0.095 |
| ***Active Agent %(g/g)*** | | 5.000 | 5.000 | 5.000 | 5.000 |
| ***Total*** | | | 100.0 | 100.0 | 100.0 |
| ***Mean Particle Size (nm)*** | | 31.6 | 20.4 | 66.3 | 157.3 |

CLAIMS

1. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine.

2. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine in the form of a micellar precursor.

3. A spontaneously dispersible pharmaceutical composition for oral administration comprising
1) N-benzoyl-staurosporine,
2) a hydrophilic component, and
2) a surfactant.

4. A composition as claimed in any one of claims 1 to 3 comprising a lipophilic component.

5. A composition as claimed in any preceding claim wherein the hydrophilic component comprises 1,2-propylene glycol or a polyethylene glycol.

6. A composition as claimed in any preceding claim comprising ethanol as a hydrophilic co-component.

7. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant selected from the group consisting of polyoxyethylenes, polyglycerols and related polyols, and polyalkylene oxide copolymers.

8. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a

polysorbate.

9. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant having a HLB value of greater than 10 and a co-surfactant having a HLB value of less than 10.

10. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a polysorbate, and a transesterified ethoxylated vegetable oil as a co-surfactant.

11. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant having a HLB value of greater than 10 and fatty acid glyceride as a lipophilic component.

12. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a polysorbate, and a lipophilic component selected from the group consisting of a fractionated coconut oil, a corn oil glyceride, and a acetylated mono- or diglyceride.

13. A spontaneously dispersible pharmaceutical composition for oral administration comprising

(a) up to 20% by weight of N-benzoyl-staurosporine,
(b) 5 to 50% by weight of a hydrophilic component,
(c) 5 to 80% of a surfactant or surfactant mixture,
(d) 5 to 85% of a lipophilic component, and
(e) 0.05 to 5 % of an additive.

14. A method of treatment comprising administering a dispersible pharmaceutical composition according to any preceeding claim to a subject in need of such

treatment.

15. A composition substantially as hereinbefore described with reference to the Examples.

16. Use of N-benzoylstaurosporine in the manufacture of a medicament suitable for oral administration.